REMARKS

Applicant respectfully request reconsideration of the present application in view of the accompanying evidence and the reasons that follow.

I. Status of the claims

No claims are newly added, cancelled, amended or withdrawn. A listing of claims is provided solely for the convenience of the Examiner.

Claims 1-28 and 34 were previously cancelled, and claims 30, 32, 33, 37 and 40 were previously withdrawn pursuant to an election of species. Applicant respectfully requests rejoinder and examination of the withdrawn claims upon identification of allowable subject matter in the generic or linking claims.

Following entry of the foregoing amendments, claims 29-33 and 35-42 are pending, and claims 29, 31, 35, 36, 38, 39, 41 and 42 are under examination. Claim 29 is the sole independent claim under examination.

II. Priority and withdrawal of the rejections over Okuda

Applicant thanks the Examiner for acknowledging the perfection of the claim to priority, giving the present claims an effective filing date of December 19, 2003. In view of the perfected priority, the Examiner withdrew the rejections under 35 U.S.C. § 102(a), § 102(e) over U.S. Patent Application Publication No. 2006/0251653 to Okuda ("Okuda"). The Examiner also withdrew rejections under 35 U.S.C. § 103(a) as allegedly rendered obvious by Okuda in view of Hirohata *et al.* "Elevation of cerebrospinal fluid interleukin-6 activity in patients with vasculitides and central nervous system involvement," *Clin. Immunol and Immunopath* 66:225-229 (1993) ("Hirohata"). Accordingly, all prior bases of rejection are overcome.

III. Rejection under U.S.C. § 103

A. The rejection

The Examiner newly rejects claims 29, 31, 38, 39, 41 and 42[1] under 35 U.S.C. § 103(a) as allegedly rendered obvious by the combination of:

- Ito et al., "Preventives or remedies for psoriasis containing as the active ingredient IL-6 antagonist," U.S. Patent No. 7,320,792 ("Ito").
- Hirohata et al., "Elevation of cerebrospinal fluid interleukin-6 activity in patients with vasculitides and central nervous system involvement," *Clin. Immunol and Immunopath* 66:225-229 (1993) ("Hirohata").
- Noris et al., "Interleukin-6 and RANTES in Takayasu arteritis," *Circulation* 100: 50-60 (1999) ("Noris").

Ito is cited for teaching that psoriasis is associated with elevated IL-6 levels, and that psoriasis is treated by the administration of monoclonal antibodies against the IL-6 receptor. Hirohata and Noris are cited for their teaching that vasculitis is associated with an elevated level of IL-6. The Examiner combines these references to argue that:

> the person of ordinary skill in the art would be motivated to use Ito's antibodies to treat vasculitis or Takayasu arthritis, and would have had a reasonable expectation of success in view of the teachings of Hirohata and Norris that both polyarteritis nodosa and Takayasu arthritis are closely associated with elevated IL-6 levels.

Applicant respectfully traverses the rejection for the following reasons.

B. The motivation provided by Ito is limited to psoriasis

Ito demonstrates that antibodies that bind to the IL-6 receptor inhibit IL-6 signalling, and is effective for the treatment of psoriasis. The fact that such antibodies are effective against psoriasis does not mean that such antibodies would be effective in treating vasculitis, a different disease. The motivation must come, instead, from evidence that IL-6 causes

[1] Claims 35 and 36 are not listed as either rejected, but also are not listed as allowed. Applicant requests clarification, but will assume for this response that the Examiner intended to reject claims 35 and 36 under the same basis as claims 29, 31, 38, 39, 41 and 42.

vasculitis, and that blocking IL-6 would treat vasculitis. This motivation is lacking from Ito, and is also not provided by Hirohata and Noris.

C. Hirohata and Noris only demonstrate a correlation

Hirohata shows that the level of IL-6 is increased in patients with vasculitis having nervous system involvement. The more recent publication by Noris also describes a relationship between vasculitis and IL-6, and describes IL-6 as a useful *marker* for disease activity. Noris considers that IL-6 is a useful marker for the presence of activated lymphocytes, which are believed to be central to the disease. *See* Noris, page 57, col. 2 to page 58, col. 1. While both references teach a strong correlation between IL-6 and disease, neither reference teaches or suggests that vasculitis would be treated by inhibition of IL-6, such as by the administration of an antibody that binds to the IL-6 receptor.

D. Teaching away: IL-6 inhibits inflammation

It is error to rely on correlation to infer causation, especially regarding cytokines. Indeed, earlier reports demonstrated that IL-6 inhibits inflammation. *See* Ulich et al., "Intratracheal injection of endotoxin and cytokines. II. Interleukin 6 and transforming growth factor beta inhibit acute inflammation," *American Journal of Pathology*, 1991, Vol.138, No.5, 1097-1101, ("Ulich"), previously provided by Applicant. Ulich states that "Interleukin-6 also is shown to be endogenously upregulated within the lung after intratracheal challenge with endotoxin, providing evidence that IL-6 may represent an endogenous negative feedback mechanism to inhibit endotoxin-initiated cytokine-mediated acute inflammation." *Id.* Abstract. Ulich continues to explain that "[t]he mechanism of the anti-inflammatory action of IL-6 and TGF β may relate to the ability of these cytokines to inhibit TNF α (and as shown by the present data) and IL-1 production by macrophages. Host-derived IL-6 is upregulated locally after challenge with LPS and may act as an endogenous negative feedback mechanism to inhibit the LPS-initiated IL-1 and TNF-mediated acute inflammatory process." (page 1100, col. 2, emphasis added).

In summary, Ulich demonstrates that IL-6 is highly expressed during inflammation, and acts through negative feedback to repress the inflammation mediated by IL-1 or TNFα.

Accordingly, the correlation between IL-6 and inflammatory conditions does not suggest that IL-6 causes inflammation, but the reverse: that inflammation causes IL-6 to be released to *treat* inflammation. In such a context, blocking IL-6 would be expected not to treat disease, but exacerbate it.

Assuming a specific causality from a correlation between a cytokine and disease, and acting to treat the disease by blocking the cytokine can, therefore, be harmful. Such a situation has been demonstrated for TNF. For example, "blockage of TNF activity was found to increase the amount of edema formation in both the pulmonary and pancreatic microvascular beds," according to Guice et al. "Anti-tumor necrosis factor antibody augments edema formation in caerulein-induced acute pancreatitis," J. *Surg. Res.* 1991, Vol 51, 495-499 ("Guice," copy attached). Similar results were described by Murata, et al., "Possible implications of cytokines in the pathophysiology of acute pancreatitis," *Saishin Igaku*, 47(11) 49-56, 1992 ("Murata," English translation previously provided). Murata states that "administration of anti-TNF antibody in cerulein-induced pancreatitis augmented not only pancreatic edema but also pulmonary lesions. The inhibition of the TNF action by the pretreatment prevents from transmitting the abnormality called cerulein-induced pancreatitis to the body's defensive system. In other words when rats themselves try to complete the inflammatory reaction by their own defense system, the first step signal, TNF cannot transmit its signal to the next one. As the result, anti-inflammatory reactions cannot be taken place so that pancreatic inflammation becomes severe, and pancreatic inflammation itself is aggravated more by severe local tissue lesions. Thus it is considered that pulmonary lesions were developed by a cytokine network without a TNF-mediated pathway." *See* Murata page 10, lines 10 to 23 of English translation. Murata continues at page 12, lines 2 to 8 "Many cytokines overlap in their biological activities. Furthermore, one cytokine controls the induction of another kind of cytokine and modifies its activity, thereby the body's defense response to an invasion has been controlled complicatedly and elaborately. Therefore, it may be meaningless that the pathophysiology of SIRS is explained only by the involvement of one or two kinds of cytokines." Finally, "It is important that the induction of cytokines by an invasion such as pancreatitis is the body's normal defense response. Thus the inhibition of all

the cytokine reactions may conversely aggravate inflammation." Murata, page 13, lines 3 to 7.

Thus, cytokines that *correlate* with inflammation may not actually be anti-inflammatory, or at least have an important role in the normal anti-inflammatory reactions that serve to control the immune response. As a result, inhibiting those cytokines may not only fail to treat a disease, it may actually exacerbate the disease, as was demonstrated by Guice and Murata.

Turning back to IL-6 in vasculitis, Hirohata and Noris both report that IL-6 is strongly correlated with vasculitis, and is a marker for disease severity. Such a result is not inconsistent with IL-6 having an antiinflammatory role in vasculitis. Further, just as Noris describes IL-6 as indicating the presence of activated lymphocytes that are believed to cause vasculitis, Murata (pages 5-6) emphasizes the importance of activated lymphocytes in pancreatitis. However, when Murata blocked a supposed pro-inflammatory cytokine produced by activated lymphocytes (TNF), the disease was exacerbated, not treated. Thus, when Noris describes IL-6 production as a marker of activated lymphocytes in vasculitis, there is a logical basis for the person of ordinary skill to believe that blocking IL-6 would not only *not treat* vasculitis but, in view of Murata and Ulich, would actually *worsen* the disease.

Thus, the art teaches away from administration of an antibody against the IL-6 receptor to treat vasculitis in a person in need.

E. A reasonable expectation of success is required to establish obviousness for methods of treating a disease

Even *without* the teaching away set forth above, the cited art fails to render obvious the claimed invention. The requirement for a "reasonable expectation of success" reflects the key role of unpredictability in determining obviousness under *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). The requirements for predictability to sustain a rejection under § 103 are much higher in unpredictable arts, "*when the combination requires a greater expenditure of time, effort, or resources* than the prior art teachings" according to the USPTO's September 1, 2010, supplemental guidelines concerning *KSR Int'l Co. v. Teleflex Inc.*, 550

U.S. 398 (2007) (emphasis added). What is considered "reasonable" must also be considered from the perspective of the person of ordinary skill. In the context of the presently claimed method of treating a human disease, the person of ordinary skill is a physician.

A physician would require a *very* strong evidence of efficacy before treating a human with a serious illness, like vasculitis. Mere correlations are insufficient in a situation where an erroneous assumption could further harm or kill the person. This is not mere speculation: as demonstrated by the above references, blocking supposedly pro-inflammatory cytokines greatly exacerbated inflammatory disease. Yet, with vasculitis, all that is shown is a correlation. No evidence is provided to demonstrate causation, or the blocking IL-6 would treat vasculitis. The present art fails to meet the high standard of predictability that is necessary to sustain an obviousness rejection, therefore.

F. The art demonstrates that the field is unpredictable

Even *if* the Examiner asserts that the "reasonable expectation of success" is lower than asserted by Applicant, the cited art still fails to render obvious the claimed invention because there is considerable evidence of unpredictable in the field.

Prior to the priority date of the present application, it was well known that cytokines such as IL-6 form a complicated network, and for example, the following were known:
1. A cytokine exhibits various biological actions (Pleiotropy);
2. A plurality of cytokines exhibit the same action on the same cell (Redundancy); and
3. A plurality of cytokines are involved in the same cell line depending on the process of differentiation and growth.

These points are made by Murata, for example.

The existence of such a complicated cytokine network makes it not only difficult to predict an in vivo effect from an in vitro experimental result, but to tease out the relevant contribution of a given cytokine to a disease. Even *if* a specific cytokine is identified as a cause of disease, it does not follow that blocking the cytokine would treat the disease. Simply put, this can only be determined by experimental evidence in human or animal models.

For example, while administration of TNF induced pulmonary edema (Hocking et al., "Mechanism of pulmonary edema induced by tumor necrosis factor-α," *Circulation Research* 1990, 67, 68-77, copy attached), Guice demonstrated that administration of anti-TNF antibody in cerulein-induced pancreatitis augmented not only pancreatic edema but also pulmonary edema. Thus, despite clear evidence that TNF caused edema in the absence of other disease, in the presence of disease, blocking TNF not only did not reverse edema but worsened it.

There is, therefore, great unpredictability in applying the correlations described in the prior art to a reasonable expectation of success in treating vasculitis by administration of an antibody against the IL-6 receptor.

G. Summary

The Examiner asserts that "the person of ordinary skill in the art would be motivated to use Ito's antibodies to treat vasculitis or Takayasu arthritis, and would have had a reasonable expectation of success in view of the teachings of Hirohata and Norris that both polyarteritis nodosa and Takayasu arthritis are closely associated with elevated IL-6 levels." This conclusion relies on several errors of fact and law.

Hirohata and Noris only show a correlation between IL-6 and vasculitis. They, with Noris, do not teach that administration of antibodies against the IL-6 receptor would treat vasculitis. The art has shown that correlation between cytokines and disease are such that it not only wrong to assume a particular causality, but that inhibition of the cytokine may not only fail to treat the disease, but actually worsen it. Thus, not only is there great unpredictability in extrapolating from the prior art to the claims, but the evidence of actual harm arising from incorrect assumptions raises the standard of "reasonableness" very high. A mere correlation is, at most, an invitation to further experimentation in animals, but is insufficient to enable a method of treatment in humans. Because a person of ordinary skill would not have the requisite reasonable expectation of success, the prior art does not render obvious the claims.

CONCLUSION

Applicant believes that all rejections are overcome, and that all claims under examination are allowable. An early notification to this effect is sought. Applicant further request that the Examiner rejoin and examine withdrawn claims 30, 32, 33, 37 and 40.

Examiner Spector is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to credit any overpayment, or charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or any missing fees, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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